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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,818	04/26/2001	Anthony Steven Weiss	GHC11USA	8602

270 7590 05/16/2006

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 05/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,818	WEISS, ANTHONY STEVEN	
	Examiner	Art Unit	
	Holly Schnizer	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46,48,49,52,54,57,90 and 92-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46, 48-49, 52, 54, 57, 90, and 92-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2-17-06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/17/06 has been entered.

Status of the Claims

Claims 46, 48-49, 52, 54, 57, 90, and 92-114 are currently pending and have been considered in this Office Action.

Claim Objections--(Withdrawn)

The objection of Claims 60 and 61 for the recitation of "aa" instead of amino acid is withdrawn in light of the cancellation of the claims.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The present rejection below has been modified from the previous Office Action due to the amendment of the claims. The claims have been amended to limit the method to reducing susceptibility of tropoelastin to serine proteases comprising mutating specific regions of SEQ ID NO:4. However, susceptibility of tropoelastin to any given serine protease could not be reduced by merely mutating a particular serine protease cleavage site because the tropoelastin is susceptible to cleavage by many different serine proteases with different recognition sequences. For example, the Specification indicates that trypsin digestion of tropoelastin was very extensive and, given enough time, resulted in complete degradation (p. 51, lines 1-3). Thus, making a mutation in the serine protease recognition sequence RAAAGLG might reduce susceptibility of tropoelastin to thrombin and kallikrein cleavage *at that site* (it would not reduce overall susceptibility to thrombin and kallikrein cleavage because they recognize more than one sequence as shown in Table 1) but there is no evidence that it would reduce susceptibility of tropoelastin to trypsin cleavage. Thus, the enablement rejection is maintained for reasons cited in the previous Office Actions and herein. The rejection as modified to address the amendments appears below. A response to Applicants arguments follows the rejection.

Rejection:

Claims 46, 48-49, 52, 54, 57, 90, and 92-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing the susceptibility of tropoelastin to thrombin, kallikrein, trypsin, plasmin, gelatinase B, or serum by mutating the sequences described in the Specification (see

Table I for example), does not reasonably provide enablement for a method for reducing the susceptibility of a tropoelastin to proteolysis by *any serine* protease comprising mutating *any* sequence of those listed in the claims in the tropoelastin so that the susceptibility of the tropoelastin to any serine protease is reduced. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation would be required to characterize all of the possible protease cleavage sites in tropoelastin so that the full scope of the claimed method could be practiced with a reasonable expectation of success. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The *nature of the invention* involves the finding of potential cleavage recognition sites in the tropoelastin sequence for thrombin, kallikrein, trypsin, plasmin, gelatinase B, and serum by digesting tropoelastin with each protease and sequencing the resulting peptide fragments.

The *breadth of the claims* is so broad as to encompass reduction of the susceptibility of tropoelastin to cleavage by any serine protease by mutating a sequence within the regions of residues 1-8, 1-9, 1-12, 78-86, 81-89, 152-160, 441-451, 515-521,

564-574, or 593-605 of SEQ ID NO:4 in tropoelastin that results in eliminating the cleavage by any serine protease.

The *state of the prior art and relative skill of those in the art* is such that those of skill in the art were aware that serine proteases were involved in the processing of tropoelastase. For example, Mecham et al. (references AY, AZ, and AAR of IDS filed May 24, 2001) describe an enzyme that cleaves tropoelastin with a trypsin like specificity. Hayashi et al. (ref. AW) of IDS filed May 24, 2001) describe a 45 kD tropoelastin degradation product processed by a metal protease. And, Romero et al. (ref. AAT of IDS filed May 24, 2001) teaches that calcium dependent proteases, kallikrein, trypsin, and elastase are effective in the degradation of tropoelastin but that the major source of proteolytic activity in serum was not clear. There is no teaching or suggestion in the art of mutating protease cleavage sites contained in tropoelastin in order to decrease susceptibility to protease cleavage. In addition, there are innumerable proteases with unique sequence specificities such that any protein can be completely degraded with a combination of non-specific proteases (for example, pronase, a mixture of non-specific proteases from S. griseus is often used to give complete proteolysis; see Voet and Voet, Biochemistry N.Y., John Wiley & Sons, 1990, p. 116.

The Specification provides *guidance and examples* of resulting peptide sequences after tropoelastin digestion with thrombin, kallikrein, trypsin, plasmin, gelatinase B, and serum (see Table I). The Specification does not provide any examples of a specific tropoelastin wherein a protease cleavage is reduced or

eliminated by mutation of a protease cleavage site. The Specification and claims do provide guidance as to what specific protease cleavage sequences and which amino acids within those sequences could be mutated. For example, the specification and claims indicate that susceptibility of tropoelastin to thrombin, kallikrein, or serum cleavage could be reduced by mutating the sequence RAAAG at position 515 in the human tropoelastin sequence (see Table I and claims) and more specifically by replacing arginine with alanine. Thus, given the examples summarized in Table I and the guidance in the Specification, these methods involving mutating specific sequence to result in reduced susceptibility to specific protease cleavage are considered enabled.

Given the lack of knowledge about tropoelastin susceptibility to proteases other than those tested in the present Specification and their recognition sites in tropoelastin, it would be highly unpredictable as to what sequences other than those described in the Specification could be mutated to reduce protease susceptibility.

Therefore, for the reasons given above, the quantity of experimentation required to practice the claimed method commensurate in scope with the claims is considered undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of all the proteases that cleave tropoelastin and the cleavage recognition sites in order to reduce the susceptibility of tropoelastin to proteolysis. It is this additional characterization constitutes undue experimentation.

Applicants argue that the specification provides at least 33 exemplary sequences which may be mutated to reduce the susceptibility of tropoelastin to proteolysis by a serine protease and that in light of this disclosure there is no undue experimentation. This argument has been considered but is not deemed persuasive for the following reasons.

While the specification identifies some potential serine protease cleavage sites in tropoelastin, the specification does not identify all sequences in tropoelastin that are susceptible to serine protease cleavage. Even for the proteases studied, the Specification admits that not all the plasmin and trypsin-produced peptides were able to be identified unambiguously (see p. 54, lines 26-27 of Specification). In addition, page 61 states, "All the peptides sequenced confirmed that cleavage occurred after a Lys or Arg as expected for many serine proteases (Keil 1992). However, tropoelastin contains a large number of Lys and Arg yet only a small number of these residues were actually recognized and cleaved"(p. 61, lines 24-29). Table 1 represents about 11 unique protease recognition sequences (some sequences are repeated because they appear to be recognized by more than one protease), 5 of which are represented in SEQ ID NOs: 8-12. The sequences of SEQ ID NOs: 17-44 are 8 sequences of 8 amino acids representing the single serine protease recognition sequence, RAAAG, wherein each sequence has one or two substitutions of amino acids not required for protease recognition. Second, as explained above, mutation of a serine protease cleavage site would not reduce the susceptibility of tropoelastin to proteolysis by any serine protease because it would have the same susceptibility to all proteases that recognize different

cleavage sites than the one mutated. For example, kallikrein (a serine protease) appears to cleave at the following sequence: R/SLSPELREGD (see Table 1). However, this sequence is not cleaved by thrombin (another serine protease). Therefore, mutating the protease recognition site, RSLSPELREGD, might reduce susceptibility of tropoelastin to kallikrein cleavage (see Table 1) but not to thrombin cleavage because thrombin would continue to cleave at its own unique protease cleavage sites. Thus, for the reasons described above and in the previous Office Actions, the rejection is maintained.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46, 48-49, 52, 54, 57, 90, and 92-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to include regions of specific amino acid sequence that can be mutated. However, there is no support in the Specification for the particular ranges claimed. There is no support for making mutations specifically at one or more residues corresponding to residues specifically within positions 1-8, 1-9, 1-12, 78-86, 81-89, 152-160, 441-451, 515-521, 564-574, or 593-605 of SEQ ID NO:4. It is noted that the Specification does provide support for replacing arginine at position 515 with an alanine. However, Claim 93 is rejected because it is not limited to this one substitution and may still have additional mutations at the positions listed in Claim 46 from which it depends. Similarly for Claims 112 and 113, a mutation at ALAAA sequences, which occurs at positions 593-597, is supported in the Specification (p. 14, lines 25-26), however, the claim is drawn to this mutation in addition to others found in the regions listed in Claim 98 that are not supported in the Specification. Thus, the claims are rejected.

Claim Objections

Claims 112 and 113 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 98 from which they depend is limited to mutations at positions 1-9, 152-160, and 515-521 of SEQ ID NO:4, yet Claims 112-113 contain an additional limitation of a mutation at positions 593, 595, 596, or 597, is outside the regions given in Claim 98. Thus, the claims are improperly dependent. Applicant is required to cancel the claim(s), or amend

the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 105 is objected to for grammatical error in the phrase, "mutating any of the residue 515-521". This could be rewritten as "mutating any of residues 515-521" to overcome this objection.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday-Thursday from 10 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
May 14, 2006

HOLLY G. SCHNIZER, PH.D.
PATENT EXAMINER